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09/494,096	01/28/2000	Gary A. Bannon	HS 102	3034

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	

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22

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/494,096	BANNON ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 37-67 are pending.

2. The following new grounds of rejections are necessitated by the amendment filed 9/16/02.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 37-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a nucleotide molecule encoding a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M, (2) a nucleotide molecule encoding a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, (3) a nucleotide molecule encoding a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A, P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A, (4) the said nucleotide molecules wherein at least one amino acid has been modified in all the IgE epitopes of the unmodified peanut allergen, (5) the nucleotide molecules mentioned above wherein the at least one IgE eipitope is one that is recognized when the unmodified food allergen is contacted with a pool of sera IgE taken from a group at least two individuals that are allergic to the unmodified peanut allergen, (6) the nucleotide molecules mentioned above wherein at least one modified amino acid is located in the center of the at least one IgE epitope, (7) the nucleotide molecule mentioned above wherein at least one hydrophobic amino acid in the at least one IgE epitope of the unmodified peanut

allergen has been substituted by a neutral or hydrophilic amino acid, (8) the nucleotide molecule mentioned above wherein the modified peanut allergen activates T cells, (9) A vector comprising the nucleotide molecule selected from the group consisting of (a) the nucleotide molecule encoding a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M, (b) the nucleotide molecule encoding a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and (c) the nucleotide molecule encoding a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A, P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for expression in a host cell for making recombinant peanut allergen Ara h 1, Ara h 2 and Ara h3 for diagnostic assays and immunotherapy, does not reasonably provide enablement for *any* nucleotide molecule encoding *any* modified food allergen as set forth in claims 37-67 for genetically engineered plants and animals that elicit less of an allergic response than the naturally occurring organisms, or treating any allergy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only three isolated nucleotide molecules consisting of SEQ ID NOS: 1, 3 and 5 of peanut allergens Ara h 1, Ara h 2 and Ara h3, respectively, vector and host cell for producing recombinant Ara h 1, Ara h 2 and Ara h3 polypeptides consisting of SEQ ID NOS: 2, 4 and 6, respectively (See page 18). The specification discloses that only the specific amino acid substitution within the IgE binding epitope of Ara h1 polypeptide of SEQ ID NO: 2 such as the ones listed in Table 4 would lead to a reduction in IgE binding. Likewise, a specific single amino acid substitution within the IgE binding epitope of Ara h2 polypeptide of SEQ ID NO: 4 such as the ones listed in Table 5 would bind less IgE and stimulate T cell than unmodified recombinant Ara h2. Again, only the specific amino acid substitution such as the ones listed in Table 6 within the IgE epitope of Ara h3 polypeptide of SEQ ID NO: 6 would bind less IgE for recombinant allergen for desensitization immunotherapy. The specification further discloses three modified peanut allergens whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M, a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and another modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A, P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy.

Other than the specific polynucleotide molecules encoding the specific modified peanut allergen mentioned above for producing the modified allergen, there is insufficient guidance as to which nucleotides, the corresponding amino acid in at least one IgE epitope of which food allergen has been modified such as substitution, deletion, or addition and whether the resulting polynucleotide encoding a modified food allergen has reduced IgE binding and increase T cell proliferation, in turn, would be useful for desensitization immunotherapy, and/or genetically engineered plants and animals that elicit less of an allergic response than the naturally occurring organisms. Given the indefinite number of undisclosed nucleotide molecule encoding any

modified food allergen, any modified food allergen such as legumes, milks, grains, eggs, fish, crustaceans, mollusks, wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp, there is insufficient working example demonstrating that any nucleotide molecule encoding any modified food allergen is effective for treating any allergy. Even if the nucleotide molecule is limited to modified peanut allergens, there is no in vivo working example using polynucleotide for treating peanut allergy (gene therapy). Further, there is no showing in the specification as filed that any genetically engineered plants and animals ever made using any nucleotide molecule encoding any modified food allergen such as peanut allergens.

Ferreira *et al*, of record, teach nucleotide molecules for site-directed mutagenessis in a gene encoding a protein such as the major hazel pollen allergen Cor a 1/16 which yields a modified allergen Cor a 1/16 T10 that fails to be less reactive with IgE wherein the modified hazel pollen allergen comprises at least one amino acid change such as proline to threonine (See page 128, DNA construct, Table 1, T1 P10 to T, page 132, third paragraph from bottom, in particular). It is known in the art that even a single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. Fasler *et al.* (PTO 892) teach that peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral Asn residue at position 173 with a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine also did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular). Burks *et al.* (PTO 892) teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Stanley et al (PTO 892) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley et al

also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular). Colman *et al* teach that a single amino acid changes within the interface of antibody-antigen complex can abolish the antibody-antigen interaction or binding entirely (See page 33, in particular). Since there is no obvious position within each polypeptide that, when mutated, would result in loss of IgE binding, it follows that the specific nucleotides within the polynucleotide molecule that encode said polypeptide (modified allergen) would require guidance. Given the indefinite number of undisclosed nucleotide molecule, it is unpredicatable which undisclosed polynucleotide molecule that encodes a modified allergen that is less reactive with IgE, or no longer binds IgE and activates T cells, in turn, would be useful for producing the modified allergen for desensitization immunotherapy. Given the lack of guidance as to which amino acid residues in the at least one IgE epitopes of which food allergen based on which protein from a source such as the ones recited in claims 45-46, and 55 has been modified, i.e., substitution for neutral or hydrophilic amino acid, it follows that the nucleotide molecules encoding the undisclosed food allergen are not enablement. Since the nucleotide molecules encoding any modified food allergen are not enabled, it follows that the undisclosed nucleotide molecules in the vector for expression in a host cell are not enabled. It also follows that the undisclosed nucleotide molecule encoding the modified food allergen wherein the modified food allergen activates T cells is not enabled. Even if the nucleotide molecule is limited to peanut allergen, Fasler *et al.* teach that substituting a neutral Asn residue at position 173 with a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine, the corresponding nucleotide encoding the modified peanut allergen fails to induce T cell proliferation and cytokine production (activated T cell). Given that the nucleotide molecule encoding the modified food allergen protein is not defined and there is no guidance as to which nucleotide position within said gene encoding an amino acid sequence that comprises at least one IgE binding site, the success of predicting which nucleotide molecule after modification would yield a modified allergen having at least one amino acid substitution so that the modified allergen no longer binds IgE but activates T cells is null.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention as broadly as claimed without undue amount of experimentation. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. As such, further research would be required. In view of the quantity of experimentation necessary, the insufficient number of working examples, the unpredictability of the art, the insufficient guidance and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicants' arguments filed 9/16/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) while it is true that the examples presented in the specification related to peanut allergens, the specification clearly states that its teachings are applicable to other protein allergens. (2) the inventive demonstration that such as anaphylactic food allergen protein can be modified so that IgE binding is reduced as compared with the unmodified protein provides a strong teachings to those of ordinary skill in the art other nucleotide molecules encoding appropriately modified protein allergens can also be made. (3) post-art references (exhibited A-D) show that the methods taught in the present application have been successfully applied to non-peanut allergens.

However, the claimed invention encompassed any polynucleotide molecule encoding any modified food allergen; the claims are not drawn to a method of screening and making modified food allergen. The specification only enables for a nucleotide molecule encoding a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M, (2) a nucleotide molecule encoding a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, (3) a nucleotide molecule encoding a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A, P248A; E249A;

E252A; Q253A; F246A; F250A; L251A; A254L and F255A for making the modified recombinant peanut allergen Ara h 1, Ara h 2 and Ara h3 for diagnostic assays and immunotherapy.

The specification does not teach how to make and use any other polynucleotide molecule encoding any modified food allergen. Since the polynucleotide, the corresponding amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. reduced IgE binding and stimulates T cell) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting which amino acid within the polypeptide reduces IgE binding and stimulates T cell, in turn, the polynucleotide encoding the modified food allergen for treating allergy is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant application, it is noted that various substitutions and the like provide a range of activities, not all which are necessarily predictive of reducing IgE binding and stimulate T cell proliferation. See page 21, lines 12-13 of the specification for example. In fact, Stanley et al (PTO 892) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley et al also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Fasler *et al.* (PTO 892) teach that peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral Asn residue at position 173 with a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine also did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly

reduced proliferative responses and cytokine production by T cells (page 524, in particular). Burks *et al.* (PTO 892) teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Because of the lack of sufficient guidance and predictability in determining which modifications would lead to reduce IgE binding and enhance T cell proliferation for treating any allergy using the undisclosed polynucleotide and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.), it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of other polynucleotide molecule encoding infinite number of undisclosed modified food allergen with reduced ability to bind IgE and stimulated T cell proliferation. Without sufficient guidance, the changes which can be made in the structure of food allergen, the corresponding polynucleotide encoding the modified food allergen and still provide reduced ability to bind IgE and enhanced T cell activation is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. A person of skill in the art could not predict which particular amino acid within the amino acid sequences of which food allergen are essential and could be modified, in turn, the polynucleotide molecule encoding the undisclosed allergen could be used in immunotherapy.

With regard to post date references, none of the references disclose polynucleotide molecule encoding the modified food allergen. Further, none of the modified food allergens, the corresponding nucleotides in the references were enablement at the time the invention was filed. Finally, the claims are drawn to polynucleotide and are not drawn to a method of screening and making modified food allergen.

5. Claims 37-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any nucleotide molecule as set forth in claims 37-67 for genetically engineered plants and animals that elicit less of an allergic response than the naturally occurring organisms, or treating any allergy.

The specification discloses only three isolated nucleotide molecules consisting of SEQ ID NOS: 1, 3 and 5 of peanut allergens Ara h 1, Ara h 2 and Ara h3, respectively, vector and host cell for producing recombinant Ara h 1, Ara h 2 and Ara h3 polypeptides consisting of SEQ ID NOS: 2, 4 and 6, respectively (See page 18). The specification discloses that only the specific amino acid substitution within the IgE binding epitope of Ara h1 polypeptide of SEQ ID NO: 2 such as the ones listed in Table 4 would lead to a reduction in IgE binding. Likewise, a specific single amino acid substitution within the IgE binding epitope of Ara h2 polypeptide of SEQ ID NO: 4 such as the ones listed in Table 5 would bind less IgE and stimulate T cell than unmodified recombinant Ara h2. Again, only the specific amino acid substitution such as the ones listed in Table 6 within the IgE epitope of Ara h3 polypeptide of SEQ ID NO: 6 would bind less IgE for recombinant allergen for desensitization immunotherapy. The specification further discloses three modified peanut allergens whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 2 (Ara h1) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid Q at position 143 has been substituted for A (Q143A), P144A; R145A; K146A; I147A; R148A; P149A; E150A; G151A; R152A; Q143M; P144M; R145M; K146M; I147M; R148M; E150M; G151M; and R152M, a modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 4 (Ara h2) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acids at position 20, 31, 60 and 67 has been substituted for alanine, and another modified peanut allergen whose amino acid sequence is substantially identical to that of an unmodified peanut allergen of SEQ ID NO: 6 (Ara h3) except that at least one amino acid has been substituted in at least one IgE epitope wherein the amino acid T at position 247 has been substituted for A, P248A; E249A; E252A; Q253A; F246A; F250A; L251A; A254L and F255A for diagnostic and immunotherapy.

With the exception of the specific polynucleotide molecules encoding the specific modified peanut allergen mentioned above, there is inadequate written description about the structure associated with function of *any* nucleotide molecule encoding *any* modified food allergen, *any* modified food allergen based on *any* protein obtained from legumes, milks, grains, eggs, fish, crustaceans, mollusks, *any* protein obtained from a source such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean, shrimp, or even peanut allergens such as Ara h1, Ara h2 and Ara h3 the following reasons: (1) the specific SEQ ID NO is not recited in the claims. (2) there are inadequate written description about which amino acids in at least one IgE epitope of which undisclosed food allergen to be modified or substituted, in turn, the corresponding nucleotide molecule encoding the undisclosed food allergen has reduced IgE binding and activates T cell as compared to any unmodified food allergen for making any modified food allergen, let alone for genetically engineered plants and animals that elicit less of an allergic response than the naturally occurring organisms, or treating any allergy using the polynucleotide (gene therapy). Even if the polynucleotide molecule is limited to peanut allergen, there is insufficient written description about the structure because "polynucleotide molecule" without SEQ ID NO has no structure, much less which amino acid in which IgE epitope is modified so that the modified allergen has reduced IgE binding and activates T cells.

The specification discloses only polynucleotide molecules encoding three proteins such as Ara h1, Ara h2 and Ara h3 from only peanut (Arachis hypogaea). Given the lack of a written description of *any* additional representative species of polynucleotide molecule encoding any modified food allergen, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 9/16/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the specification itself clearly states that its teachings are applicable to other unmodified food allergen such as references that list known amino acid sequences, nucleotide sequences, and IgE epitope for a wide variety of unmodified food allergens

from cow milk, egg, codfish, hazel nut, soybean, and shrimp. (2) the specification teaches methods of identifying IgE binding sites.

However, the claims are drawn to any nucleotide molecule encoding any *modified* food allergen. With the exception of the specific polynucleotide molecules encoding the specific modified peanut allergen mentioned above, there is inadequate written description about the structure associated with function of *any* nucleotide molecule encoding *any* modified food allergen, *any* modified food allergen based on *any* protein obtained from legumes, milks, grains, eggs, fish, crustaceans, mollusks, *any* protein obtained from a source such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean, shrimp, or even peanut allergens such as Ara h1, Ara h2 and Ara h3 the following reasons: (1) the specific SEQ ID NO is not recited in the claims. (2) there are inadequate written description about which amino acids in at least one IgE epitope of which undisclosed food allergen to be modified or substituted, in turn, the corresponding nucleotide molecule encoding the undisclosed food allergen has reduced IgE binding and activates T cell as compared to any unmodified food allergen for making any modified food allergen, let alone for genetically engineered plants and animals that elicit less of an allergic response than the naturally occurring organisms, or treating any allergy using the polynucleotide (gene therapy). Even if the polynucleotide molecule is limited to peanut allergen, there is insufficient written description about the structure because "polynucleotide molecule" without SEQ ID NO has no structure, much less which amino acid in which IgE epitope is modified so that the modified allergen has reduced IgE binding and activates T cells.

The specification discloses only polynucleotide molecules encoding three proteins such as Ara h1, Ara h2 and Ara h3 from only peanut (Arachis hypogaea). Given the lack of a written description of *any* additional representative species of polynucleotide molecule encoding any modified food allergen, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

6. Claims 37, 47, 56-60 and 62-66 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The "1-6 amino acid residues" in claims 56 and 62 represents a departure from the specification and the claims as originally filed.

The "1-5 amino acid residues" in claims 57 and 63 represents a departure from the specification and the claims as originally filed.

The "1-4 amino acid residues" in claims 58 and 64 represents a departure from the specification and the claims as originally filed.

The "1-3 amino acid residues" in claims 59 and 65 represents a departure from the specification and the claims as originally filed.

The "1-2 amino acid residues" in claims 60 and 66 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out where the supports for said phrases come from.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 41-42 and 51-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "at least one hydrophobic amino acid" in claims 42 and 52 has no antecedent basis in base claims 41 and 51, respectively. Base claims 41 and 51 recite at least one amino acid in at least one IgE epitope of the unmodified food allergen has been modified.

9. The filing date of the instant claims is deemed to be the filing date of provisional applications 60/074,590 filed 2/13/98; 60/074,624 filed 2/13/1998; 60/074,633 filed 2/13/1998 and 60/073,283 filed 1/31/1998. It is noted that priority applications USSNs 09/106,872 and 08/717,933 were not available to the examiner at this time. Therefore, the examiner could not determine whether the instant claims have priority to said applications. If applicant desires priority prior to 1/31/1998, applicant is invited to point out and provide documentary support for

the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 37-45, and 47-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burks *et al* (of record, Eur. J. Biochem. 245: 334-339, April 1997; PTO 892) in view of Evens *et al* (Therapeutic Drug Monitoring 15: 514-520, 1993; PTO 892).

Burks *et al* teach modified food allergen whose amino acid sequences are substantially identical to that of an unmodified food allergen such as Ara h1 such as the ones listed in Table 1 and Fig 3 except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified peanut allergen Ara h1 (See entire document, Fig 1B, Fig 3, Abstract, in particular). The reference IgE epitope is being one that is recognized by a pool serum from 15 patients which is at least two individual with peanut hypersensitivity when the unmodified food allergen is contacted with serum IgE the individuals that is allergic to the unmodified food allergen (See Figure 2A, in particular). The reference modified food allergen wherein one amino acid has been modified such as Ala or glyccine substitution in all the IgE epitope (See Fig 3 and Figure 5, in particular). The reference IgE epitope of peanut allergen is recognized when contacted with a pool of sera such as IgE taken from a group of 10 individuals that are allergic to the unmodified

food allergen such as peanut (See page 337, Figures 4-5, in particular). The reference modified amino acid is located in the center of at least one IgE epitope (See amino acids that are underline in Table 1, page 336, in particular) and the amino acid has been modified by substitution of Alanine that is hydrophobic or glycine, which is neutral (See Figure 6, in particular). Claim 43 and 53 are included in this rejection because the functional property such as stimulates T cell proliferation is an inherent property of the reference modified Ara h 1 peptide fragments. Claim 45 is included in this rejection because the reference modified peanut allergen such as Ara h1 is a protein obtained from legumes. The reference modified IgE epitopes of peanut allergen has 1-6 amino acids been modified (See underline amino acid sequence of reference peptide 1 in Table 1, in particular). The reference modified IgE epitopes of peanut allergen has 1-5 amino acids been modified (See underline amino acid sequence of reference peptide 16 in Table 1, in particular). Claims 58-60 and 64-66 are included in this rejection because the recitation of "1-4, 1-3, and 1-2 amino acid residues have been modified" is an obvious variation of teachings of the reference. Burks *et al* teach further teaches that the hypogenic Ara h1 peptide fragments are useful for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph, in particular).

The claimed invention in claims 37-43, 45, 47-53, and 55-67 differs from the teachings of the reference only that the nucleotide encoding a modified food allergen.

The claimed invention in claim 44 differs from the teachings of the reference only that the nucleotide encoding a modified food allergen in a vector for expression in a host cell.

The claimed invention in claim 54 differs from the teachings of the reference only that the nucleotide encoding a modified peanut allergen in a vector for expression in host cell.

Evans *et al* teach that because the DNA codons (triplets) for each amino acid already are known, the DNA sequence or nucleotide molecule is then synthesized in reverse from the protein of interest (See page 515, column 2, first full paragraph, Table 1, in particular). The nucleotide encoding the protein of interest is made so that nucleotide can be put into a vector such as plasmid and host cells to scale up the production of the protein of interest (See page 516, column 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to synthesize the nucleotide molecule in reverse from the modified food allergen such as peanut allergen Ara h1 as taught by Burks *et al* so that nucleotide molecule can be put into a vector such as plasmid and host cells to scale up the production of the modified

allergen as taught by Evens *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Evans *et al* teach that the nucleotide encoding the protein of interest can be put into a vector such as plasmid and host cells to scale up the production of the protein of interest (See page 516, column 1, in particular). Burks *et al* teach further teaches that modified food allergen such as the hypogenic Ara h1 peptide fragments are useful for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph, in particular).

13. Claims 37-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley *et al* (Archives of Biochemistry and Biophysics 342(2): 244-253, June 1997; PTO 1449) in view of Evens *et al* (Therapeutic Drug Monitoring 15: 514-520, 1993; PTO 892).

Stanley *et al* teach modified food allergen whose amino acid sequences are substantially identical to that of an unmodified food allergen such as Ara h2 except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified food allergen is reduced as compared with IgE binding to the unmodified peanut allergen Ara h2 (See entire document, Fig 2, Abstract, in particular). The reference IgE epitope is being one that is recognized by a pool serum from 15 patients which is at least two individual with peanut hypersensitivity when the unmodified food allergen is contacted with serum IgE the individuals that is allergic to the unmodified food allergen (See Figure 2, in particular). The reference modified food allergen wherein one amino acid has been modified such as Ala or glyccine substitution in all the IgE epitope (See Table III and Figure 5, in particular). The reference IgE epitope of peanut allergen is recognized when contacted with a pool of sera such as IgE taken from a group of 15 individuals that are allergic to the unmodified food allergen such as peanut (See caption in Figure 5, in particular). The reference-modified amino acid is located in the center of at least one IgE epitope (See amino acids that are underline in reference peptide 6 and 8, Table III, in particular) and the amino acid has been modified by substitution of Alanine, which is hydrophobic, or glycine, which is neutral (See Figure 5, in particular). Claim 43 and 53 are included in this rejection because the functional property such as stimulates T cell proliferation is an inherent property of the reference modified Ara h 1 peptide fragments. Claim 45 is included in this rejection because the reference modified peanut allergen such as Ara h2 is a protein obtained

from legumes. The reference modified IgE epitopes of peanut allergen has 1-6 amino acids been modified (See underline amino acid sequence of reference peptides 6 and 8 in Table II, in particular). Claims 57-60 and 63-66 are included in this rejection because the recitation of "1-5, 1-4, 1-3, and 1-2 amino acid residues have been modified" is an obvious variation of teachings of the reference. Claim 46 is included in this rejection because the modified food allergen Ara h2 amino acid sequence is homologous to a protein obtained from wheat (See Table II, in particular). Stanley *et al* teach further teaches that the hypogenic Ara h2 peptide fragments are useful for the purpose of diagnostic and immunotherapy (See page 252, first paragraph, in particular).

The claimed invention in claims 37-43, 45, 47-53, and 55-67 differs from the teachings of the reference only that the nucleotide encoding a modified food allergen.

The claimed invention in claim 44 differs from the teachings of the reference only that the nucleotide encoding a modified food allergen in a vector for expression in a host cell.

The claimed invention in claim 46 differs from the teachings of the reference only that the nucleotide wherein the modified food allergen is based on wheat.

The claimed invention in claim 54 differs from the teachings of the reference only that the nucleotide encoding a modified peanut allergen in a vector for expression in host cell.

Evans *et al* teach that because the DNA codons (triplets) for each amino acid already are known, the DNA sequence or nucleotide molecule is then synthesized in reverse from the protein of interest (See page 515, column 2, first full paragraph, Table 1, in particular). The nucleotide encoding the protein of interest is made so that nucleotide can be put into a vector such as plasmid and host cells to scale up the production of the protein of interest (See page 516, column 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to synthesize the nucleotide molecule in reverse from the modified food allergen such as peanut allergen Ara h2 as taught by Stanley *et al* so that nucleotide molecule can be put into a vector such as plasmid and host cells to scale up the production of the modified allergen as taught by Evens *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Evans *et al* teach that the nucleotide encoding the protein of interest can be put into a vector such as plasmid and host cells to scale up the production of the protein of interest (See page 516, column

1, in particular). Stanley *et al* teach further teaches that the hypogenic Ara h2 peptide fragments are useful for the purpose of diagnostic and immunotherapy (See page 252, first paragraph, in particular).

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 37-45, 47, and 53-67 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, and 7 of U.S. Patent No. 6,486,311 B1 (Nov 2002; PTO 892). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons:

(1) Claim 1 of the '311 patent recites an isolated nucleotide molecule encoding the peanut allergen designated Ara h II hybridizing under standard conditions to SEQ ID NO: 1 and which encodes a protein binding to anti-Ara h II antibodies from patients with peanut allergies while claim 7 of the '311 patent recites the said nucleotide molecule wherein the peanut allergen comprises one or more mutated IgE epiotpes. Therefore, claims 1 and 7 of the '311 patent includes the limitations in the instant claim 37-43, 45, 47, 53 and 55-67 because a species of the nucleotide molecule encoding the modified food allergen such as peanut Ara h II anticipates a genus of nucleotide molecule encoding the modified food allergen of instant claims 37-43, 45, 47, 53 and 55-67. Further, the isolated nucleotide of instant claims would also hybridize to the isolated nucleotide molecule encoding the peanut allergen in the '311 patent (claims 1-3) because

the instant nucleotide molecule encoding a modified food allergen whose amino acid sequence is substantially identical to that of an unmodified food allergen such as SEQ ID NO: 1 of the '311 patent or the modified SEQ ID NO: 1 of the '311 patent.

(2) Claim 4 of the '311 patent recites the said isolated nucleotide molecule encoding the modified peanut allergen is inserted into a vector for expression in an appropriate host. Therefore, claim 4 of the '311 patent includes the limitation of instant claims 37, 44, 47 and 54 which recite the nucleotide molecule encoding a modified food allergen such as peanut allergen in a vector for expression in a host cell.

16. No claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

19. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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July 28, 2003

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